The Healthy Pituitary

Introduction

This lesson establishes the anatomy, histology, and physiology necessary for mastering pituitary disease and lays the foundation for the endocrine diseases that follow in this module. This lesson focuses on the hypothalamus, posterior pituitary, and anterior pituitary, covering anatomy, embryology, the specialized vasculature of the portal system, and the cell types of the pituitary and the hormones they secrete. The details of each hormone and axis are going to be discussed where they belong in the rest of the module. This lesson is merely a warm-up.

Gross Anatomy

The pituitary gland is commonly taught as being composed of glandular epithelial tissue (anterior pituitary, aka adenohypophysis) and neurosecretory tissue (posterior pituitary, aka neurohypophysis). In this model, the hypothalamus is a completely disconnected structure somewhere in the brain. That is true if you evaluate the structure surgically. The one pituitary gland sits in the sella turcica, formed by the sphenoid bone, and has one vascular supply. A surgeon can remove the one pituitary gland. However, as we will explore in the embryology section that follows this one, that is a completely inappropriate structural and physiologic representation. Instead, the visual we want you to form in your mind is that there is one neural organ—the hypothalamus-posterior pituitary (one organ)—and one glandular organ—the anterior pituitary (a different organ).

The **hypothalamus** and the **posterior pituitary** are the **same organ**. The neuron cell bodies of the **supraoptic nucleus** and the **paraventricular nucleus** are in the hypothalamus. They have unmyelinated axons that project into the posterior pituitary. The nerve terminals of those neurons house vesicles with hormones in them. The neurons of the supraoptic nucleus synthesize **antidiuretic hormone** (ADH) at the cell body, located in the hypothalamus, then transport that protein in vesicles along the microtubules, down to their nerve terminals in the posterior pituitary. The neurons of the paraventricular nucleus synthesis **oxytocin** at the cell body, located in the hypothalamus, then transport that protein in vesicles down to their nerve terminals in the posterior pituitary. The hypothalamus does more than these two endocrine functions, but you must see the posterior pituitary as an extension of the hypothalamus and not the back of the pituitary. The posterior pituitary can be artificially divided into two regions: the pars nervosa and the infundibulum. The **pars nervosa** is the entire posterior pituitary. It is where the terminal axons rest and from where the hormone is released. The pars nervosa is connected to the hypothalamus by the **infundibulum,** through which the axons run. The infundibulum is continuous with the **median eminence** of the hypothalamus.

The hypothalamus is more than just where the neuron cell bodies of the posterior pituitary reside. Additional nuclei perform various functions outside of the scope of this lesson, such as heat regulation. The hypothalamus also acts as the regulatory control center for the anterior pituitary. The anterior pituitary releases hormones that target specific organs. The hypothalamus tells the anterior pituitary what hormones to release. The hypothalamus communicates to the anterior pituitary by releasing trophic hormones into the local portal vasculature, as discussed in the vasculature section below.

The **anterior pituitary** is a separate, distinct organ from the hypothalamus-posterior pituitary. There are three anatomic areas of the anterior pituitary, termed the pars distalis, pars intermedia, and pars tuberalis. The names are frustrating because they do not immediately communicate what they do. The vast majority of the anterior pituitary is the glandular epithelium, called the **pars distalis.** The **pars tuberalis** is the top of the anterior pituitary, which wraps around the infundibulum of the posterior pituitary. The **pars intermedia** is the epithelium that separates the posterior pituitary and anterior pituitary. It begins as the lining of Rathke's pouch (discussed next). When that lumen involutes, the side that lines the neurohypophysis and the side that lines the adenohypophysis merge to form one layer, the pars intermedia.

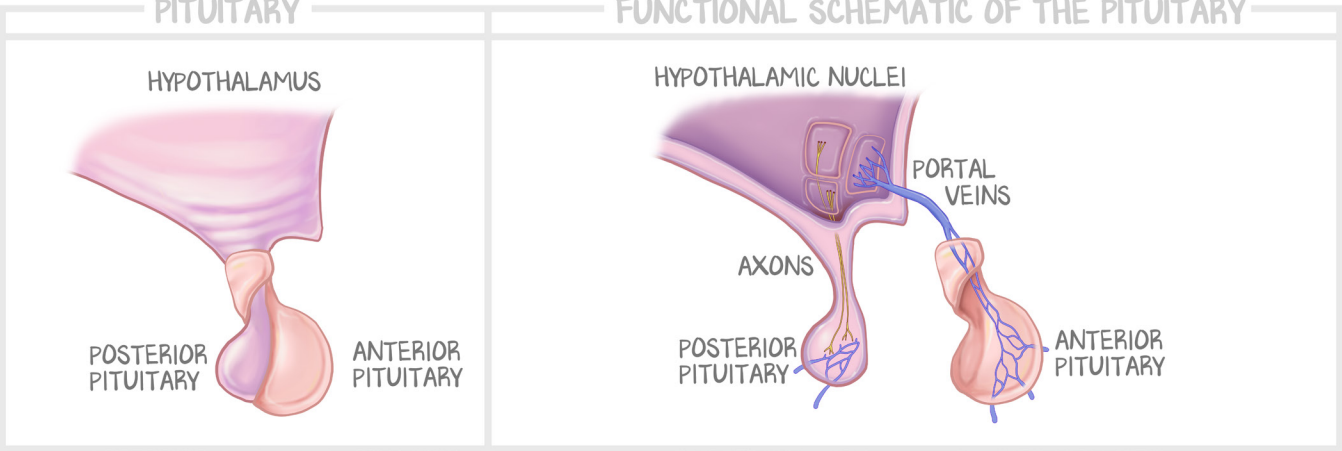

Figure 2.1: The Pituitary Glands
The classic representation of the pituitary gland depicts anterior and posterior lobes that are named as one organ due to their location in the sella turcica. The color-coding signifies that the hypothalamus and posterior pituitary are of the same tissue, and the anterior pituitary is of a different tissue. But because both the anterior and posterior "pituitary" release hormones in the capillaries of the sella turcica, they were believed to be one organ. However, the functional schematic of the pituitary reveals that each lobe is a separate organ, a separate gland: the neurons of the hypothalamus project axons into the posterior pituitary (making it actually hypothalamus), and the anterior pituitary receives inputs from the hypothalamus through a portal vein.

The pars intermedia is defined by colloid-filled follicles lined with cuboidal cells, with histology that is similar to that of the thyroid. The purpose of this tissue is yet to be elucidated, but it demonstrates an obvious separation from the very glandular anterior pituitary (distalis) and the very sparsely populated posterior pituitary (nervosa). In lower organisms, this region of the pituitary produces a hormone that changes the pigment of fur, feathers, etc. in response to variations in light, perceived by the hypothalamus.

Embryology

The anterior and posterior pituitary are not the front and back of the same gland. They are from distinctly different embryologic origins and are not continuous. Their embryologic origins demonstrate that they are actually a combination of two distinct organs that happen to share an anatomic location and vascular supply within the sella turcica. Embryologically and physiologically, they are completely different organs.

The **posterior pituitary is hypothalamic tissue**. The neurons of the hypothalamus are within the supraoptic and paraventricular nuclei in the hypothalamus proper. The axons of those neurons travel down the infundibulum and terminate in the posterior pituitary. The hypothalamus and posterior pituitary are derived from **neuroectoderm**. The growth downward forms the infundibulum, and subsequently, the pars nervosa. The hypothalamus grows down into the sphenoid bone from the third ventricle. The hypothalamic growth is the posterior pituitary.

The **anterior pituitary** is its own tissue. It is derived from **oropharynx ectoderm** and grows up into the sphenoid bone. The invagination of the ectoderm creates a lumen that is continuous with the oropharyngeal lumen. This lumen is called **Rathke's pouch**. The connection between the oropharynx and Rathke's pouch degenerates around week 6 of development, both the ectodermal and luminal connections to the oropharynx having been severed by the closure of the sphenoid bone. Rathke's pouch persists, a lumen within the anterior pituitary surrounded by oropharynx ectoderm. Rathke's pouch is supposed to eventually involute entirely, being filled in by the proliferation of the cells that will become the pars intermedia of the anterior pituitary, although the pouch sometimes persists as a pituitary cleft, a space that physically separates the anterior pituitary from the posterior pituitary. The ectoderm that

touches the posterior pituitary will become the pars intermedia. The ectoderm that doesn't becomes the pars distalis, except for the very top of the anterior pituitary, which wraps around the infundibulum of the posterior pituitary, forming the pars tuberalis.

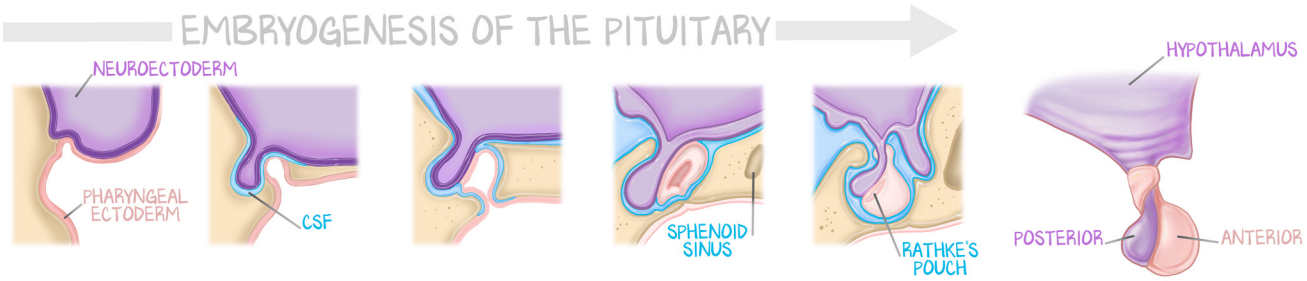

Figure 2.2: Embryogenesis of the Pituitary Gland
The neuroectoderm grows downward into the developing sphenoid bone, continuous with the hypothalamic neural tissue. At the same time, the oropharynx ectoderm grows up into the developing sphenoid bone. The lumen of the oropharynx is continuous with the lumen made by the evagination of the anterior pituitary. As the sphenoid bone develops, it severs the connection between the oropharynx and the anterior pituitary. Rathke's pouch, the lumen, is obliterated as the anterior pituitary grows up against/into and wraps around the posterior pituitary.

A normal, healthy variant of this development is called **empty sella syndrome**. The pituitary should form in the sella turcica of the sphenoid bone. The sella forms irrespective of the pituitary. Because the anterior pituitary migrates upward, and the posterior pituitary is the hypothalamus, the anterior pituitary may migrate too far up, and join the posterior pituitary above the sella turcica. These patients are totally normal. The condition is discovered when an MRI is performed of the brain for something else.

Vasculature

Two arteries supply the pituitary gland. The arteries directly irrigate the neural tissue—infundibulum and posterior pituitary—and do not directly irrigate the anterior pituitary. The pituitary gland is also called the hypophysis, separated into the adenohypophysis (the anterior lobe) and the neurohypophysis (the posterior lobe). The blood vessels that irrigate and drain them are named after the pituitary gland's formal name and thus are named the hypophyseal vessels. Follow along with Figure 2.3 for the next few paragraphs.

The **superior hypophyseal arteries** are derived from both the internal carotid arteries and the posterior communicating arteries from the circle of Willis. These arteries reach up to irrigate the hypothalamus and down to irrigate the infundibulum. The **inferior hypophyseal arteries** are derived from the internal carotid arteries and reach up to irrigate the posterior pituitary. The **hypophyseal veins** drain both the anterior and posterior pituitary glands. Each gland has its own vein, and they eventually coalesce into the internal jugular vein. The hypophyseal arteries irrigate neural tissue only. The hypophyseal veins drain both pituitary glands. What about the supply to the anterior pituitary? And what about drainage from the hypothalamus? Before we get there, let's discuss the posterior pituitary.

The **posterior pituitary** has a network of **fenestrated** capillaries that allow for the release of hormones stored within vesicles in the axon terminals. These axon terminals release hormones directly into the capillary network, which drains into the hypophyseal veins and, eventually, the jugular vein. The fenestrations minimize the barrier to diffusion of the hormones released. ADH and oxytocin are water-soluble proteins, and so cannot diffuse through an endothelial cell membrane. Thus, the fenestrations allow for the release of the hormones and direct access to the venous system. Being dropped into the venous system also ensures that the hormone will be delivered to the heart before any other organ, thus ensuring equal distribution throughout the body.

The **anterior pituitary** also has a network of **fenestrated** capillaries that allow for the release of hormones stored within vesicles of cells in the anterior pituitary. Just as in the posterior pituitary, exocytosis of these vesicles releases water-soluble hormones into the venous system: different hormones, same capillary structure. The main distinction is that the hypothalamus-posterior pituitary is irrigated by arteries. The anterior pituitary has no direct arterial supply but instead receives blood through **hypophyseal portal veins** that connect the hypothalamic and anterior pituitary capillary beds.

The hypothalamus (as the posterior pituitary) releases water-soluble hormones into fenestrated capillaries that will eventually drain into veins and be spread systemically. The hypothalamus (as the hypothalamus) also releases water-soluble hormones into fenestrated capillaries that drain into veins, but these veins are destined for the anterior pituitary and conjoin to form the hypophyseal portal vein, which then reopens into another fenestrated capillary network around the anterior pituitary. This enables the hypothalamus to release trophic hormones meant only for the cells of the anterior pituitary into its capillary bed and ensure that those hormones will be delivered directly to their target cells.

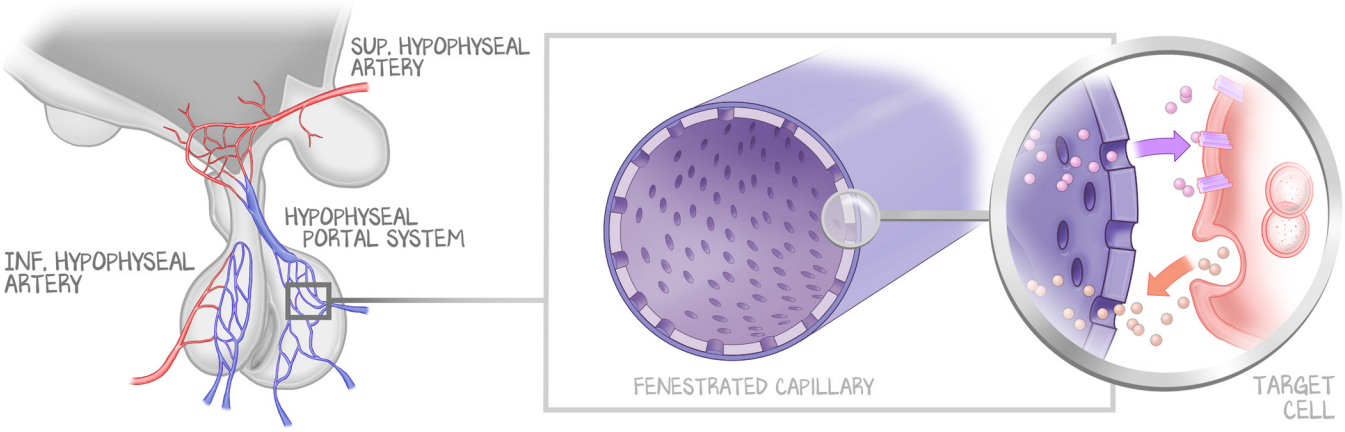

Figure 2.3: Vasculature of the Pituitary Glands
The superior hypophyseal arteries arise from the internal carotid and the posterior communicating arteries to feed the hypothalamus. The inferior hypophyseal arteries arise from the internal carotid and feed the posterior pituitary. There are three distinct, fenestrated capillary networks—one around the hypothalamus, one around the anterior pituitary, and one around the posterior pituitary. The hypothalamic capillaries drain into a hypophyseal portal vein, and that vein becomes the anterior pituitary capillaries. Several hypophyseal veins drain the posterior pituitary separately from the anterior pituitary, but all converge at the internal jugular. Inset: fenestrations allow for the rapid release of water-soluble hormones into the venous circulation.

Hypothalamic-Pituitary Axes and Feedback Inhibition

We're going to talk generally at first, offering a representational view demonstrating patterns and similarities. Once that is taken care of, we'll touch on the two exceptions.

There are five hypothalamic-pituitary axes. There are five hypothalamic hormones, each with its own unique hormone receptor. There are five types of cells in the anterior pituitary, each of which releases a different type of anterior pituitary hormone. Each cell type possesses a hormone receptor that matches a specific hypothalamic hormone. Each type of cell in the anterior pituitary has only one type of receptor and can listen to only one hypothalamic signal.

That means that each axis is contained within itself. Each axis has a hypothalamic hormone, hypothalamic hormone receptor, anterior pituitary cell, anterior pituitary hormone, anterior pituitary hormone receptor, effector organ, and hormone made by that effector organ. The hypothalamus's default is to release hormone; the hypothalamus will increase the release of hormone until it's inhibited by the

downstream hormone of the axis. The cells of the anterior pituitary and effector organs are off by default and will not make or release their hormone until instructed to do so by the hormone that stimulates them. This is **positive feedforward** regulation. The hypothalamus releases its hormones and stimulates the cells of the anterior pituitary. The anterior pituitary releases its hormones, which stimulate the effector organs. With only one exception, down the axis is stimulatory—**feedforward down the axis.**

Each axis regulates itself with **negative feedback**. The products of the anterior pituitary cells inhibit the release of the hypothalamic hormone that stimulated their production. The products of the effector organ cells inhibit the release of the hypothalamic hormone that started the cascade, as well as inhibit the release of the anterior pituitary hormone that stimulated the effector hormone's release.

Let's try this again with an example. Don't worry if you don't know the abbreviations yet. Just follow the pattern. The hypothalamus releases CRH into the hypophyseal portal system. CRH binds to the CRH receptors of cells in the anterior pituitary. Without that receptor activation, that cell was doing nothing. CRH receptor activation leads to the production of ACTH from the anterior pituitary cells. ACTH travels to the adrenal gland, where it binds to and activates ACTH receptors on the cells of the adrenal gland. The adrenal gland cells do nothing until ACTH tells them to. The adrenal gland cells make cortisol. ACTH is a product of CRH receptor stimulation. Cortisol is a product of ACTH receptor stimulation. That's feedforward. ACTH also binds ACTH receptors on the hypothalamus, which inhibits CRH release. Cortisol binds to cortisol receptors in both the hypothalamus and anterior pituitary cells. Cortisol inhibits the release of CRH and ACTH. That's feedback.

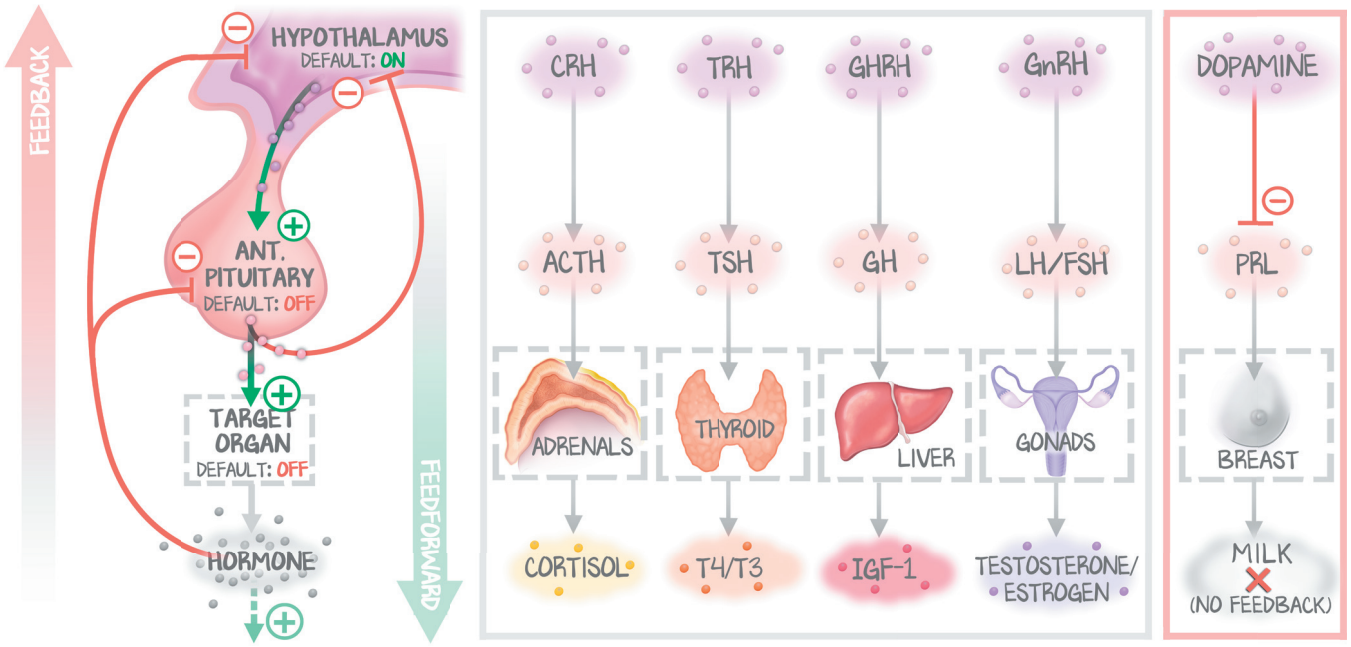

Figure 2.4: Hypothalamic-Pituitary Axis
On the left, we see the generalization of positive feedforward and negative feedback. Hormones released "down the axis" are positive feedforward, stimulating the cells of the target organ to produce its hormone. Whether it is hypothalamic hormones on the anterior pituitary or anterior pituitary hormones on the effector organ, the signal is stimulatory. The hormones produced by the anterior pituitary or the effector organ have an intended effect outside the axis. But within the axis, these hormones act to inhibit the cells of the organs before it—negative feedback. Anterior pituitary hormones inhibit the hypothalamic cells, and the effector organ hormones inhibit the hypothalamus and the anterior pituitary. "Inhibits the organ" really means "inhibits the cells of the hypothalamus or anterior pituitary that secrete the positive feedforward hormones of the axis." The rest of the illustration gives an overview of all the systems, including the exception of prolactin.

There are two exceptions: growth hormone and prolactin (both are explored in detail in the next lesson.) First, growth hormone. The hypothalamus releases two hormones in regard to growth hormone: stimulatory GHRH and inhibitory somatostatin. The downstream hormones of the axis both stimulate somatostatin release and inhibit GHRH release. The second is prolactin. The hypothalamus secretes an inhibitory hormone instead of a stimulatory one. The prolactin-making cells of the anterior pituitary are on by default and require inhibition by hypothalamic hormones. Prolactin does not have an effector organ that releases another hormone. Instead, prolactin instructs the cells of the mammary glands to make milk. As the milk will be expressed, there is no feedback mechanism.

Cell Types of the Anterior Pituitary

There are five cell types of the anterior pituitary, which correspond to the five hormones released by the anterior pituitary. Each is stimulated by the hypothalamus through a unique hormone specific to the cell type. In the next few paragraphs, we are going to describe the five cell types of the anterior pituitary, which hypothalamic hormone induces each to release its hormone, how many of that cell type there are, which hormone each type releases, and what the target organ is for each anterior pituitary hormone. The details are covered in subsequent lessons. This should serve as an orientation.

Figure 2.5: Cells of the Pituitary
(a) Electron microscopy showing neurosecretory granules in the axon terminals of the neurons in the pars nervosa. (b) Light microscopy showing the transition from the pars nervosa (left) to the pars distalis (right), and the brief stint of colloid-filled follicles of the pars intermedia. (c) Light microscopy of a normal anterior pituitary demonstrating a mix of hormone-secreting cells with fenestrated capillaries between them.

You may see the cells referred to as "cell type-tropes" and "cell type-trophs." We have chosen to use "-trope" instead of "-troph," but either is appropriate. We present these cell types starting with the most abundant in the anterior pituitary and working down to the rarest. The first two have the most complicated regulation and are the exceptions mentioned at the end of the last section.

Somatotropes make up approximately 50% of the anterior pituitary. Don't try too hard to make sense of the next two sentences but do read them. Somatotropes make somatotropin and are inhibited by somatostatin. Somatropin induces the liver to make somatomedin, through which its downstream effects occur. All that "somatostuff" makes things confusing. Thankfully, medical science agreed, and

so developed better names for the cells and hormones of this axis. You will definitely still see the "somatostuff" used in the literature, so you should be familiar with it. But let's go ahead and state the opening sentences in this paragraph with terms that make more sense. **Growth hormone-secreting** cells (GH cells, somatotropes) secrete **growth hormone** (GH, aka somatotropin), are stimulated by hypothalamic **growth hormone-releasing hormone** (**GHRH,** arcuate nucleus), and are inhibited by hypothalamic **somatostatin** (paraventricular nucleus). GH targets the **liver** to make **insulinlike growth factor-1** (IGF-1, somatomedin), which induces growth. The details of these cells are discussed in Pituitary #2: *The Unhealthy Anterior Pituitary.* GHRH positively feedforwards GH, which positively feedforwards IGF-1. GH and IGF-1 negatively feedback; IGF-1 stimulates somatostatin release and inhibits GHRH release.

Lactotropes (PRL cells) make up 15–20% of the pituitary. Lactotropes make the hormone **prolactin** (**PRL**). Lactotropes represent a unique regulation within the anterior pituitary. The hypothalamus normally secretes trophic signals to stimulate the cells of the anterior pituitary to release the corresponding pituitary hormone. In the case of lactotropes, the hypothalamus secretes a **prolactin-inhibiting** hormone—**dopamine**. The hypothalamus releases dopamine into the portal circulation, which in turn inhibits lactotropes. The absence of the hypothalamic signal disinhibits lactotropes, allowing them to secrete prolactin. Prolactin acts on the mammary glands of the breast, **stimulating breast milk secretion**. Unlike the other hormones from the anterior pituitary, the activity of prolactin does not induce the release of another hormone and therefore has no feedback-inhibition loop. Prolactin stimulates milk secretion, but it is **oxytocin** (posterior pituitary) that induces the contraction of myoepithelial cells, which expresses the milk from its origin in the breast alveoli into the ducts it travels through to get to baby. Breastfeeding, the neuronal reflexes, and their regulation are discussed in detail in the Reproduction module. The consequence of prolactin oversecretion is explored in the next lesson, Pituitary #2: *The Unhealthy Anterior Pituitary*.

Corticotropes (ACTH cells) make up 15% of the anterior pituitary. They are responsible for making **adrenocorticotropic hormone** (ACTH) from a precursor called **proopiomelanocortin (**pro-opio-melano-cortin, POMC). POMC is a single amino acid sequence that many different cells produce. Each cell type (not just those in the anterior pituitary) cleaves POMC to make the protein they need. The corticotropes use POMC to make ACTH. The other cell types will be discussed later in Endocrine (melanocytes) and Neuroscience (opioid receptors). ACTH is released from corticotropes of the anterior pituitary when stimulated by the hypothalamic **corticotropin-releasing hormone** (CRH). The target of ACTH is the zona fasciculata of the adrenal gland. There, ACTH-R activation stimulates the production of **cortisol.** This hypothalamic-pituitary-adrenal axis obeys a classic feedback loop; cortisol inhibits ACTH and CRH, whereas ACTH inhibits CRH. The details of this axis are covered in Adrenal #1: *The Healthy Adrenal* and dysfunction in Adrenal #2: *Cortisol*.

Gonadotropes (FSH and LH cells) make up 10% of the anterior pituitary. They are stimulated by hypothalamic **gonadotropin-releasing hormone** (GnRH) and release **follicle-stimulating hormone** (FSH) and **luteinizing hormone** (LH). Both FSH and LH play a fundamental role in the production of gonadal testosterone and estrogen, becoming vital to the process of reproduction, which is discussed in detail in the Reproduction module.

Thyrotropes (TSH cells) make up approximately 5% of the anterior pituitary. They are responsible for making **thyroid-stimulating hormone** (**TSH**). They are stimulated by hypothalamic **thyrotropin-releasing hormone** (**TRH**). TSH is sent to the thyroid gland, where the activation of the TSH receptor stimulates the production of the thyroid hormones T_4 and T_3. In the classic hormone feedback, TSH inhibits the hypothalamic release of TRH, whereas T_3 and T_4 inhibit both TRH release from the hypothalamus and TSH release from the anterior pituitary. Thyroid hormone provides the "spark" to metabolic activity and is discussed in the Thyroid series.